Effect of dosing time on the pharmacokinetics and pharmacodynamics of sunitinib

Published: 12-07-2012
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Amendment (5-apr-2013): Dosing-time of sunitinib may alter the pharmacokinetics

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON20106

Source
Nationaal Trial Register

Health condition

Patients with advanced clear cell renal cell carcinoma, metastatic GIST or advanced p-NET treated with sunitinib

Sponsors and support

Primary sponsor: Erasmus Medical Center, Department of Medical Oncology
Source(s) of monetary or material Support: self financial research

Intervention

Outcome measures

Primary outcome

Difference in pharmacokinetics of sunitinib in morning intake compared to evening intake.

Secondary outcome

1. To investigate whether daily variation in CYP3A4 activity exists in humans based on midazolam and 4©\hydroxycholesterol pharmacokinetics and urine 4©\OHcholesterol;
2. To investigate if evening dosing of sunitinib affects the side effects of this drug;
3. To investigate the influence of single©\nucleotide polymorphisms in PK genes on the exposure to sunitinib (based on the MEC02.1002 protocol).

Study description

Background summary

Since metabolism of sunitinib is dependant of different cytochrome P450 enzymes, including CYP3A4, which in cell-lines and rodents show a circadian rhythm in expression, it is very likely that pharmacokinetics of sunitinib is time dependant. The activity of CYP3A4 probably drops in night time. Higher concentrations of sunitinib and its active metabolite may be reached when sunitinib is taken in the evening. Patients participating in this cross-over study will be followed, during two courses of sunitinib. In one of both courses, they will take sunitinib at 08.00 AM, and during the other course at 18.00 PM. During both courses, they will behospiatlized during 24 hours for pharmacokinetic measurements of sunitinib. To investigate the circadian rhythm of CYP3A4, patients will be administered a low dose of midazolam. Pharmacokinetics of midazolam and 1OH-midazolam will be measured. In addition, also the endogenous marker 4beta-hydroxycholesterol will be studied as an extra test to study CYP3A4 dynamics. After completing these two courses, patients are free to decide at wich time they will continue sunitinib intake. Amendment: Since metabolism of sunitinib is dependant of different cytochrome P450 enzymes, including CYP3A4, which in cell-lines and rodents show a circadian rhythm in expression, it is very likely that pharmacokinetics of sunitinib is time dependant. Exposure to sunitinib may therefore be influenced by dosing-time.
Patients participating in this cross-over study will be followed, during three courses of sunitinib. In one of three courses, they will take sunitinib at 08.00, one course at 18.00, and one course at 13.00 . During all three courses, they will behospiatlized during 24 hours for pharmacokinetic measurements of sunitinib.
To investigate the circadian rhythm of CYP3A4, patients will be administered a low dose of midazolam. Pharmacokinetics of midazolam and 1OH-midazolam will be measured. In addition, also the endogenous marker 4beta-hydroxycholesterol will be studied as an extra test to study CYP3A4 dynamics.
After completing these three courses, patients are free to decide at wich time they will continue sunitinib intake.

Study objective

Amendment (5-apr-2013): Dosing-time of sunitinib may alter the pharmacokinetics

Study design

2 courses of sunitinib treatment.

Intervention

1. Blood withdrawal for pharmacokinetics of sunitinib and midazolam;
2. Administration of midazolam;
3. Urine sample collection.

Contacts

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Eligibility criteria

Inclusion criteria

1. Age ¡Ý 18 years;
2. Histological or cytological confirmed diagnosis of advanced clear©\cell renal cell carcinoma, GIST or pancreatic neuro©\endocrine tumor, treated with sunitinib;
3. WHO performance score ¡Ü 1 at study entry;
4. Any stable dose of sunitinib at study entry, defined as no dose change within 3 weeks prior to pharmacokinetics;
5. Adequate hematological functions (ANC > 1.0 x 109/L, platelets > 100 x 109/L);
6. Adequate liver and renal function defined as bilirubin concentration ¡Ü 2 x ULN, AST and

ALT ¡Ü 2.5 x ULN, serum creatinin concentration ¡Ü 2 x ULN;
7. Written informed consent;
8. For patients with reproductive potential a reliable method of contraception (excluding oral contraceptives) must be used.

Exclusion criteria

1. Pregnant or child nursing patients;
2. Serious illness or medical unstable condition requiring treatment, symptomatic CNS metastasis or history of psychiatric disorder that would prohibit the understanding and giving of informed consent;
3. Major surgery within 2 weeks prior to start of the protocol;
4. Use of CYP3A4 inhibiting or inducing medication;
5. Patients who are unable to collect blood from;
6. Patients with known allergy to sunitinib or midazolam;
7. Patients unwilling or unable to give written informed consent.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-07-2012
Enrollment:	18
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	12-07-2012
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 39190
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL3378
NTR-old	NTR3526
Other	METC ErasmusMC : 12-138
CCMO	NL39931.078.12
OMON	NL-OMON39190

Study results

Summary results
Kloth et al. Relationship Between Sunitinib Pharmacokinetics and Administration Time: Preclinical and Clinical Evidence. Clin Pharmacokinet. 2015;54(8):851-8